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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,184	11/08/1999	JACK R. WANDS	04930/032001	6241

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/21/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/436,184	WANDS ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,13-15 and 39-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 13-15, and 39-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. After review and reconsideration, the finality of the Office action of Paper No. 18 is withdrawn.

2. Claims 10, 43, 51 and 59 have been amended. Claims 69-71 have been added. Claims 10, 13-15, and 39-71 are pending and under consideration.

3. The text of sections of Title 35, U.S. Code not found in this action can be found in a previous action.

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

5. The disclosure is objected to because of the following informalities: the specification contains a blank on page 6, line 16..

Appropriate correction is required.

6. Claims 10, 13-15, and 39-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to new matter

The instant claims 10, 43, 51 and 59 have been amended to recite the limitation "said nucleic acid comprising 10-50 nucleotides in length". New claim 69 has been added which also

carries this limitation. The specification as filed states "Preferably, the length is between 10-50 nucleotides, inclusive" (page 4, lines 13-14).. This is not adequate support for the limitation of "comprising" 10-50 nucleotides, as the term "inclusive" limits the fragments to fragments consisting of 10-50 nucleic acids.

Claims 51-58 are drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an AAH antisense nucleic acid which is complementary to a AAH sequence encoding a signal peptide. Claims 43-50 are drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an AAH antisense nucleic acid which is complementary to a 5' portion of an AAH coding sequence. The specification as filed contemplates anti-sense DNA which is complementary to a 5'regulatory sequence of HAAH mRNA, a sequence encoding a signal peptide or within exon 1 of the HAAH gene. This does not support the instant claims drawn to antisense nucleic acid to AAH which is not limited to HAAH. Further, it does not support claims to a 5' portion of an HAAH coding sequence, as exon-1 of HAAH differs in scope from the 5' portion of the coding region of HAAH..

(B) As drawn to written description

The instant claims are methods which depend upon the identity of the AAH protein, 5' regulatory regions controlling the AAH protein, AAH signal peptides and exon 1 of the AAH protein. The specification identifies HAAH as a human aspartyl asparaginyl beta-hydroxylase (page 1, line 22). Thus, the term AAH reads on any aspartyl asparaginyl beta-hydroxylase, and is not limited to human aspartyl asparaginyl beta-hydroxylase. The claims are thus dependent upon a genus of AAH antisense nucleic acids. With respect to the HAAH protein, the instant specification provides a written description of the protein of SEQ ID NO:2 encoded by the cDNA of SEQ ID NO:3. When given the broadest reasonable interpretation, the claims drawn to AAH also embody, in addition to AAH from any species, allelic and splice variants, as well as any 5' regulatory regions and signal peptides.. It is known in the art that HAAH undergoes post translational cleavage to produce a smaller protein (Radosevitch, U.S. 6,166,176, column 3, lines 1-10, cited in a previous Office action) but there is no written description of the fragment produced thereby. The nature of protein variants produced by allelic sequences, splice variants or post-translational processing is that they are variant structure where the structure and function of one example does not provide guidance to the structure and function of the other members of

the genus and the specification provides no teachings to describe any other members of the genus. Further, the claims encompass 5' regulatory regions and signal peptides of AAH from human non-human species. It is noted that SEQ ID NO:3 does not include said regulatory regions or signal peptides. According to these facts one of skill in the art would conclude that the applicant was not in possession of the claimed genus of AAH coding sequences or EXON1 because a description of only one member of this genus is not representative of the variants of the genus and is therefore insufficient to support the claims to a genus. Further, applicant is not in possession of a genus of 5'regulatory regions or signal peptides. Applicant has not described the regulatory region of HAAH nor a signal peptide of HAAH and the statement that the invention includes antisense nucleic acid to the 5'region of HAAH and a signal peptide is insufficient to describe the claimed genus.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.
Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the nucleic acids antisense to the 5' regulatory region of AAH, signal peptide, exon-1 or the coding sequence, per Lilly by structurally describing a representative number of species representative of each genus, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

In this case, the specification does not describe any AAH 5'regulaotry region, in a manner that satisfies the Lilly standards. The specification describes the coding regions of HAAH, and exon 1 of HAAH is known in the art. Although the specification discloses a single member of the AAH coding sequence, this does not provide a description of the genus of AAH coding sequences or EXON-1s that would satisfy the written description requirement by the standards set out in Lilly

Thus, the specification does not provide an adequate written description of the genuses of antisense nucleic acids of the genus of 5'AAH, EXON-1 or coding sequences that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed is reliant upon, it also fails to adequately describe the claimed methods.

7. Claims 10, 13-15, and 39-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claims 10, 13-15, and 40-42 are drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an AAH antisense nucleic acid comprising a sequence which is complementary to a 5'AAH regulatory sequence, said nucleic acid comprising 10-50

nucleotides. Claims 43-50 are drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an AAH antisense nucleic acid comprising a sequence which is complementary to a 5'AAH coding sequence, said nucleic acid comprising 10-50 nucleotides. Claims 51-58 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an AAH antisense nucleic acid comprising a sequence which is complementary to a 5'AAH sequence encoding a signal peptide, said nucleic acid comprising 10-50 nucleotides.. Claims 59-67 and 69-71 are drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an AAH antisense nucleic acid comprising a sequence which is complementary to a 5'AAH sequence in exon 1 of an AAH gene, said nucleic acid comprising 10-50 nucleotides.. Claim 68 embodies the methods of claims 10, 43, 51 or 59, wherein said nucleic acid is a human AAH antisense nucleic acid.

An effective therapeutic protocol for the treatment or prevention of the formation of a tumor is subject to a number of factors which enter the picture beyond simply the inhibition of expression of a single enzyme, such as aspartyl beta hydroxylase. Demonstrating the inhibition of aspartyl beta hydroxylase expression in tumor cells cannot alone support the predictability of the method for prevention of or treating said tumor growth through administration of either an antisense nucleic acid or an intrabody directed to aspartyl beta hydroxylase. Tumor growth is a complex and multiple step process that proceeds by the acquisition of successive genetic insults (A. Hagemeijer, Leukemia, 1992, Vol. 6, Suppl. 4, pp. 16-18, cited in a previous Office action). The establishment and growth of a tumor is subject to variables beyond the overexpression of a single enzyme. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type and stage of tumor and the tumor burden.

Applicant has provided a declaration of Jack R. Wands under 37 CFR 1.132, filed July 19, 2001, stating that the administration of 20-mer oligonucleotides designed to bind to the 5' regions of the AAH mRNA block the in vitro translation of HAAH mRNA and therefore the synthesis of the HAAH protein. The experiment was carried out using an in vitro cell free transcription translation assay. The declaration further states that inhibition of HAAH gene expression was inhibited in cultured neuroblastoma cells using the –6 antisense oligomer designed to bind to the 5' regulatory regions of HAAH. The declaration further asserts that the

anti-sense nucleic acids inhibited the growth and migration of Sh-SySy neuroblastoma cells, 9L glioblastoma cells, H1 cholangiocarcinoma cells, NEC cholangiocarinoma cells, RBE cholangiocarcinoma carcinoma cells, and FOCUS hepatocellular cells. All cells testes were cultured in vitro. The instant claims require the inhibition of tumor growth in a mammal. The specification teaches the use of the full length antisense HAAH cDNA as well as antisense DNA corresponding to exon 1 of the HAAH gene were used to decrease the level of expression of the HAAH polypeptide in hepatocyte carcinoma cells, and alter the morphology of the treated cells to resemble a more differentiated phenotype. The specification does not teach the decreased level of expression of the HAAH polypeptide or the alteration of cellular morphology in a tumor in situ. The specification does not teach the decreased level of expression of the HAAH polypeptide, or alterations in cell morphology in any CNS tissue, in vitro or in vivo.

It is recognized in the art that the development of clinically useful antisense strategies for disease therapy is fraught with difficulties, even when the nucleic acid sequence for the target protein is known. Antisense nucleic acids, such as antisense cDNA or antisense exons, that are large and highly charged often interact with a wide variety of untargeted cellular components causing undesirable "non-antisense effects" (A.Branch, Hepatology, 1996, Vol. 24, pp. 1517-1529, cited in a previous Office action). Antisense nucleic acids must be optimized for use in patients. Additionally, it is well know in the art that the use of modified anti-sense oligonucleotides on CNS targets are limited by the powerful ability of the blood-brain barrier to exclude such anti-sense oligonucleotide. In order to use anti-sense technology for treatment of CNS pathologies, careful consideration must be made with respect to the target nucleotide sequence within the gene of interest, the choice of backbone modifications for the oligonucleotide, and the presence of special sequence motifs which predispose the oligonucleotide to undesirable non-antisense effects (Broaddus et al, Methods in Enzymology, 2000, Vol. 314, pp. 121-135, cited in a previous Office action). The published data indicates that only a small percentage of the antisense oligonucleotides which are tested in vitro are actually effective in the reduction of the target mRNA, and that the ability of the anti-sense oligonucleotides to bind to a target mRNA cannot be predicted due to the structure and conformation assumed by individual mRNA specie (Broaddus et al, pg. 122). Further, even if the specific structure and conformation of a particular mRNA could be adequately predicted as

an isolated molecule in a protein-free environment, it would not anticipate the accessible sites for the anti-sense oligonucleotide in vivo, wherein proteins are available to bind to the mRNA thus obscuring the oligonucleotide binding sites and potentially altering the conformation of the target mRNA. Broaddus et al teaches that a highly empirical approach to the testing of candidate anti-sense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification, therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

Further, the instant method claims require that a sufficient amount of anti-sense nucleic acid be taken up by a tumor in situ so that the amount is effective in decreasing the level of HAAH protein synthesized in said tumor cells. The instant specification provides no teaches in as to the level and duration of anti-sense nucleic acids necessary to effectively inhibit tumor growth in a tumor in situ.

The instant method claims require nucleic acid sequence complementary to exon 1 of AAH, 5' regulatory regions of AAH and signal peptides of AAH. The specification as filed provides the coding sequence of HAAH. The specification does not provide 5' regulatory regions of HAAH, a signal peptide of AAH. or the more broadly claimed AAH, as drawn to other species One of skill in the art would be subject to undue experimentation, because it would be necessary to first identify the 5' regulatory regions of AAH and signal peptides of AAH necessary to practice the claimed method.

8. All other rejections and objections as set forth in Paper No. 18 are withdrawn.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
05/20/2004

Karen A. Canella

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PRIMARY EXAMINER